Remarks

I. Support for Amendments

Support for the foregoing amendments to the claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for new claims 50-58 may be found in the specification at pages 8-9, 17- and throughout the Examples. In addition, support for new claim 50 may be found in claims 1, 2 and 8 as originally filed; support for new claims 51-53 may be found in claims 10-12 as originally filed; support for new claims 54-55 may be found in claims 17 and 18 as originally filed; support for new claim 56 may be found in claim 26 as originally filed; and support for new claims 57 and 58 may be found in claims 41, 43, 45 and 46 as originally filed. Hence, the foregoing amendments to the claims do not add new matter, and their entry into the present application is respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 1-49 have been cancelled without prejudice or disclaimer, and new claims 50-58 are sought to be entered. These amendments do not add new matter. Upon entry of the foregoing amendments, claims 50-58 are pending in the application, with claims 50 and 57 being the independent claims.

III. The Claimed Invention

The invention as presently claimed is drawn to compositions comprising an ordered and repetitive antigen or antigenic determinant array. Compositions of the invention may comprise, for example, a non-naturally occurring molecular scaffold comprising a virus-like core particle linked via an organizer polypeptide (or residue thereof) to an antigen or antigenic determinant to form an ordered and repetitive antigen array. Among other applications, the compositions of the invention are useful in the production of vaccines for the treatment of infectious diseases, in the treatment of allergies, and as pharmaccines to prevent or cure cancer and to generate defined self-specific antibodies.

IV. Summary of the Office Action

In the Office Action dated June 6, 2001, the Examiner has made one objection to, and seven rejections of, the claims. Applicants respectfully offer the following remarks to overcome or traverse each element of this rejection in the Office Action.

V. The Objection to Claim 36 Is Accommodated

In the Office Action at pages 2-3, the Examiner has objected to claim 36 as being of improper dependent form for allegedly failing to further limit the subject matter of claim 35, from which claim 36 depends. By the foregoing amendments, claim 36 has been cancelled as suggested by the Examiner, thereby fully accommodating this objection. Reconsideration and withdrawal are therefore respectfully requested.

VI. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Is Traversed

In the Office Action at pages 3-4, the Examiner has rejected claims 1-4, 8, 10-12, 17, 18, 24-30 and 33-46 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. By the foregoing amendments, claims 1-49 have been cancelled, and new claims 50-58 are sought to be entered. Applicants respectfully traverse this rejection as it may be applied to new claims 50-58, in view of the foregoing amendments and the following remarks.

A. The Metes and Bounds of "Organizer"

In making this rejection, the Examiner first contends that the metes and bounds of the term "organizer" are unclear, such that the structure of the molecular scaffold in the invention as claimed is ambiguous. *See* Office Action at pages 3-4. Applicants respectfully disagree. The term "organizer" is defined in detail in the specification at page 15, lines 4-13. Although the organizer is "bound to" the core particle as pointed out in this definition, there is no requirement that the organizer be an element separate from the core particle as contended by the Examiner (*see* Office Action at page 4, lines 5-6). Indeed, by the definition provided in the specification, the organizer can be a *part* of the core particle -- all that is necessary under the definition of "organizer" in the specification is that the organizer be bound to the core particle by at least one covalent bond. However, in the working examples identified by the Examiner at page 4 of the Office Action (*i.e.*, Examples 23-25), the core particle and the organizer are specifically designed and tailor-made for preparation of a given ordered and repetitive antigen array. Hence, even if the specifically designed and tailor-made organizer

becomes a component of the specifically designed and tailor-made core particle (*e.g.*, via genetic engineering), an important feature of the presently claimed constructs is that the organizer is not a naturally occurring component of the core particle (whether or not it is an integral part of the core particle).

It must be borne in mind that, as shown in Examples 23-25, the present invention provides compositions that produce an *ordered and repetitive antigen array.* Such an ordered and repetitive antigen array results from the combination of the special technical features of the compositions recited in the independent claims as currently presented, and more particularly from the interplay between the organizer and the first and second attachment sites.

The order and repetitiveness of the antigen array of the present invention is advantageous for optimally triggering a highly efficient immune response against the displayed antigen. The presently claimed invention accomplishes this goal by conveniently enabling the practitioner to *construct* ordered and repetitive arrays of a variety of antigens or antigenic determinants for various purposes, including diagnostic and therapeutic applications. In one application, therefore, the construction and design of such ordered and repetitive antigen arrays facilitates the creation of highly efficient vaccines (*see, e.g.*, specification at page 17, lines 19-23).

The preparation of such an ordered and repetitive antigen array in accordance with the presently claimed invention is exemplified in the present specification in Examples 23-25. To this end, the design and construction of a non-natural molecular scaffold is described in Example 23, while the subsequent association of the antigens to the designed non-natural

molecular scaffold is described in Example 25. The design of this non-natural molecular scaffold, and thus, the formation of the ordered and repetitive antigen array of Example 25, involved the development of a tailored organizer (which in this example was the peptide Gly-Gly-Lys-Gly-Gly). Prior to the connection of the organizer to the core particle (in this example, the HBcAg), the subunits of the core particle were adapted to the tailored organizer by deleting two amino acids of their tip region leading to the "HBcAg-Lys" construct. The connection of the organizer and the core particle within this particular embodiment was effected by way of genetic engineering as indicated in Example 23. However, and in accordance with the definition provided in the specification, this connection was still effected by way of at least one covalent bond. The introduced lysine residue contains a reactive amino group in its side chain representing the first attachment site. Hence, in the embodiment of the invention exemplified in non-limiting Examples 23-25, the organizer is not a naturally occurring component of the core particle. As noted above, however, that the definitions of "organizer" and "core particle" in the present specification also provide for situations in which the organizer is a part (albeit a non-naturally occurring part) of the core particle.

With regard to the Examiner's statement concerning the "nucleation site" (*see* Office Action at page 4, lines 4-8), Applicants offer the following remarks. The terms "nucleation" or "nucleation site" as used in the present specification refer to nucleation used to create an ordered and repetitive antigen array. *See, e.g.*, specification at page 15, line 6, and at page 21, lines 8-9. These terms do *not* refer to the assembly of the core particle, as the Examiner has apparently taken these terms to mean. Thus, as defined in the specification at page 14, lines

13-15, "the phrase 'non-natural molecular scaffold' refers to any product made by the hand of man that may serve to provide a rigid and repetitive array of first attachment sites." Such a rigid and repetitive array of first attachment sites is ensured by the organizers, as implied by the definition of an organizer according to the invention (*see, e.g.*, specification at page 15, lines 4-16). Herein it is stated that an organizer refers to an element that is bound to a core particle by at least one covalent bond and *in a non-random fashion*, and which element provides a *nucleation site* for creating *an ordered and repetitive antigen array.*

As correctly indicated by the Examiner, the core particle refers to a rigid structure with an inherent repetitive organization. As further stated in the specification at page 12, lines 13-16, such a core particle provides a *foundation* for attachment of an organizer. The inherent repetitive organization of the rigid structure of the core particle, therefore, facilitates the formation of an ordered and repetitive antigen array since the inherent repetitive organization of the core particles provides a *foundation* for the organizer, which organizer, then, provides a *nucleation site* for creating an *ordered and repetitive antigen array.* As indicated, the organizer further ensures formation of the ordered and repetitive antigen array of the invention as presently claimed.

Accordingly, Applicants respectfully contend that based on the definition of "organizer" provided in the specification, the metes and bounds of this term would be readily understood by one of ordinary skill in the art. Reconsideration and withdrawal of this portion of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

B. The Allegedly Missing Recitations in the Claims

The Examiner also appears to contend that, while the invention seems to involve "an antigen (or hapten) which is covalently or noncovalently bound to a structured core particle, the antigen is presented on the surface of the particle in some regular, ordered spacing, and fusion proteins (where the antigen forms a continuous polypeptide with the core subunit) are excluded . . . . this is not what the claims define." Office Action at page 4, lines 11-15. Applicants respectfully disagree.

In making this contention, the Examiner appears to allege that several elements of the invention are not recited in the claims:

(a) an antigen (or hapten) covalently or noncovalently bound to a structured core particle;

(b) a presentation of the antigen on the surface of the core particle in a regular, ordered spacing; and

(c) the exclusion of fusion proteins formed between the presented antigen and the core subunit.

See Id. Applicants respectfully assert that the claims as currently presented recite all of these elements, in such a way that one of ordinary skill could readily identify and understand the metes and bounds of each of the recitations.

First, the claims as currently presented (specifically, independent claims 50 and 57) recite that the antigen or antigenic determinant (which, as one of ordinary skill would understand, could be a hapten) is "bound by at least one non-peptide bond" to the first

attachment site on the organizer, which is in turn bound to the core particle by "at least one covalent bond." Hence, the claims specifically recite element (a) identified by the Examiner above: an antigen (or hapten) covalently or noncovalently bound to a structured core particle.

Second, independent claims 50 and 57 both recite the interaction of the antigen or antigenic determinant with the molecular scaffold (comprising the core particle and the organizer) "to form an ordered and repetitive antigen array." Hence, the claims specifically recite element (b) identified by the Examiner above: a presentation of the antigen on the surface of the core particle in a regular, ordered spacing.

Finally, independent claims 50 and 57 both specify that the antigen or antigenic determinant is bound to the scaffold (through the interaction between the second attachment site on the antigen/antigenic determinant and the first attachment site on the organizer) "by at least one non-peptide bond." As one of ordinary skill would appreciate, fusion proteins by definition would involve the attachment of the antigen/antigenic determinant to the core particle/organizer via a *peptide* bond (*i.e.*, the antigen would be fused to the core particle subunit as a single continuous polypeptide). In the Office Action, the Examiner has already acknowledged that such fusion proteins are assumed to be excluded (*see* Office Action at page 4, lines 13-18). Applicants note that, by the plain language of the claims, this assumption is correct: since the antigen/antigenic determinant is bonded to the core particle/organizer by at least one *non*-peptide bond, fusion proteins are necessarily excluded from the invention as claimed. Hence, the claims specifically recite element (c) identified by the Examiner above: the exclusion of fusion proteins formed between the presented antigen

and the core subunit.

Thus, each of the elements identified by the Examiner as components in the invention are, in fact, recited in the present claims. Accordingly, Applicants respectfully contend that the claims as currently presented are not indefinite.

As the Board has held:

> [35 U.S.C. § 112, second paragraph] merely requires that the claims set forth and circumscribe a particular area with a reasonable degree of precision and particularity. The definiteness of the claim language employed must not be analyzed in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one having ordinary skill in the pertinent art.

Ex parte Moelands, 3 USPQ2d 1474, 1476 (Bd. Pat. App. Int. 1987) (citing *In re Moore*, 439 F.2d 1232 (CCPA 1971). As discussed above, the term "organizer" is specifically defined in the present specification, and is used in the claims in a manner consistent with this definition. In addition, the elements of the claimed invention identified by the Examiner in the present Office Action are, in fact, recited in the claims as currently presented. Hence, one of ordinary skill could easily determine the scope of the invention as presently claimed; claims 50-58 thus comport with the requirements of 35 U.S.C. § 112, second paragraph, as interpreted under *Moelands* and *Moore*.

In view of the foregoing remarks, Applicants respectfully assert that the present claims particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

VII. The Rejections Under 35 U.S.C. § 102 Are Traversed

In the Office Action at pages 5-7, the Examiner has rejected claims 1-4, 24, 25, 27-30, 33-37 and/or 40-44 under 35 U.S.C. §§ 102(b) or (e) as being anticipated by Quash, Ikram, Watkins, Hunter, Rock or Larocca. Applicants respectfully traverse this rejection, and assert that the claims as originally presented and as currently pending are not anticipated by the cited art, since these documents do not expressly or inherently disclose every limitation of the rejected claims. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984).

However, to expedite prosecution but not for reasons related to patentability, Applicants have cancelled claims 1-49 and have substituted therefor new claims 50-58, which correspond substantially or exactly to previously pending claims 8, 10-12, 17, 18, 26, 45 and 46. The Examiner has acknowledged that claims 8, 10-12, 17, 18, 26, 45 and 46 are not anticipated by the cited art (*see* Office Action at page 7). Therefore, Applicants respectfully assert that new claims 50-58, which correspond substantially or exactly to these claims, also are not anticipated by the cited art. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are therefore respectfully requested.

VIII. Other Matters

A. The IDS References

Applicants acknowledge the Examiner's notation at page 7 of the Office Action that the Information Disclosure Statement ("IDS") filed in the present matter on April 14, 2000,

has not been considered because the references cited in the IDS could not be located. As the Examiner has requested, replacement copies of these references (but not of the IDS or the Form PTO-1449 submitted therewith) are being filed concurrently herewith, via hand carry to the Examiner under separate cover. If further assistance with regard to location of the references is required, the Examiner is invited to contact Applicants' undersigned representative at the telephone number provided.

B. Allowable Subject Matter

Applicants acknowledge the Examiner's statement at page 7 of the Office Action that claims 8, 10-12, 17, 18, 26, 45 and 46 appear to be free of the prior art. As noted above, by the foregoing amendments, Applicants have cancelled these claims and seek to enter new claims 50-58, which correspond substantially or exactly to these claims. Accordingly, Applicants respectfully assert that claims 50-58 are in condition for immediate allowance. Early notification to this effect is solicited.

IX. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner

believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt entry and favorable consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 1-49 are cancelled without prejudice or disclaimer.

New claims 50-58 are sought to be entered.